REMARKS

Claims 19-30, 32 and 46-66 are currently pending in this application. Solely to expedite prosecution, claims 19-21, 24-30, 32, 46-50, 52-55, 58, 60, 62-63 and 66 are amended and claims 22-23, 51, 56, 57, 59, 61, 64 and 65 are canceled. Applicants reserve the right to pursue any subject matter excluded in a related continuation or divisional application. Accordingly, claims 19-21, 24-30, 32, 46-50, 52-55, 58, 60, 62-63 and 66 are currently pending. Reconsideration is respectfully requested in light of the following remarks.

Amendments to the Claims

Independent claim 19 has been amended to more clearly define the scope of the invention and to clarify that the claimed composition is a topical composition comprised of an effective inflammation alleviating amount of the mixture of Free-B-Ring flavonoids and flavans. Support for this amendment can be found throughout the Specification (see e.g., page 14, lines 4-8, which provides the composition is preferably applied topically, page 17, lines 11-14, which provides that "the method of prevention and treatment according to this invention comprises administering topically to a host in need thereof a therapeutically effective amount" (emphasis added); pages 47-48, Example 12, which demonstrates that Soliprin™ when administered topically to the skin after exposure to UV radiation reduces erythema). Claim 19 has also been amended to clarify that the pharmaceutically or cosmetically acceptable carrier suitable for administration to the skin can include a lotion, a gel, an ointment, a cream, a soap or an emulsion. Support can be found in claims 17, 34 and 44 as filed. Finally, the claims have been amended to clarify that the claimed compositions are cosmetic as well as pharmaceutical compositions.

Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 19-30, 32 and 46-59 under 35 U.S.C. § 103(a) as being unpatentable over Xu (U.S. Pat. No. 6,083,921) in view of Zhou (U.S. Pat. No. 6,319,523). The rejection is moot as to canceled claims 22-23, 51, 56, 57, 59, 61, 64

and 65. Applicant respectfully traverses this rejection to remaining claims 19-21, 24-30, 32, 46-50, 52-55, 58, 60, 62-63 and 66.

Briefly, the Examiner reasons that Xu teaches a topical pharmaceutical composition comprised of baicalin for antibacterial purposes. The Examiner acknowledges that Xu does not teach the use of the flavan catechin, but reasons that Zhou teaches a pharmaceutical composition comprised of catechin contained within a pharmaceutical composition also for antibacterial purposes. From this, the Examiner concludes that one of ordinary skill in the art would have been motivated to modify Xu's pharmaceutical composition to include the active ingredient in Zhou's composition because the combined references would create the claimed topical pharmaceutical to be used for antibacterial purposes. The Examiner further reasons that the intended use of the claimed composition does not per se patentably distinguish the composition, since such undisclosed use is intrinsic to the composition.

The Examiner bears the burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). To establish obviousness, both the elements of the claimed invention plus the motivation to combine the elements must be present in the prior art. *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (PTO Bd. App. Intf., 1988). Thus, if an element recited in the claims is not described in the cited prior art references, then *prima facie* obviousness is not established.

Section 2112 (subsection IV) of the M.P.E.P. provides that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic," citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d

1955, 1957 (Fed. Cir. 1993). Section 2141.02 (subsection V) further provides that "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established," also citing *In re Rijckaert*. In light of this standard, the rejection raised by the Examiner is discussed in detail below.

The present invention as set forth in independent claim 19, as amended, is drawn to an anti-inflammatory composition comprising (1) an effective amount of an inflammation alleviating mixture of Free-B-Ring flavonoids containing baicalin and flavans containing catechin and (2) a pharmaceutically or cosmetically acceptable carrier suitable for administration to the skin selected from the group consisting of a lotion, a gel, an ointment, a cream, a soap and an emulsion, wherein the pharmaceutical or cosmetic composition alleviates inflammation when topically applied to the skin. These novel compositions have been found unexpectedly to be effective topical agents against inflammation-related dermatological conditions.

Xu describes pharmaceutical compositions for use in preventing and treating viral and bacterial infections or for use in enhancing the immune response. The compositions taught by Xu are a pharmaceutically acceptable carrier, baicalin, chlorogenic acid and forsythiaside (claim 1). Xu does not teach or suggest a composition of matter comprised of a mixture of Free-B-Ring flavonoids and flavans. Nor does Xu teach or suggest that any of the disclosed compositions and/or compounds would be useful in the treatment of inflammatory skin conditions. Rather, Xu teaches that the disclosed compositions "are particularly suitable for treating or preventing an infection by bacteria and other viruses that affect the respiratory system." (col. 8, lines 36-41). Furthermore, there is no evidence to suggest that there would be any overlap between indications requiring the use of the compositions taught by Xu and those of the instant application. The only teaching or suggestion regarding these compositions in general or *Scutellaria* specifically is as antibacterial, antiviral and immunomodulating substances.

There is also no teaching or suggestion in the Xu reference that the disclosed compositions are suitable for non-systemic delivery to the skin. Drug products administered via the skin fall into two general categories, those applied for local action and those for systemic

effects. Local actions include those at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis." (Ueda *et al.* "Topical and Transdermal Drug Products" (May-June 2009) Pharmacopeial Forum 35(3):750-764). Xu teaches a composition for use in treatment of respiratory infections. The suggested modes of delivery of the drug are "oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, interperitoneal, intrathecal, rectal, and vaginal administration." (Col. 10, lines 37-44). In order to treat respiratory infections, all of these modes of administering, with the exception of aerosols, are intended for systemic delivery. Topical aerosol drug formulations do not include topical carriers such as lotions, creams and gels etc. As noted by the Examiner, Xu does provide for vaginal delivery of the composition via a gel, paste or cream etc., however, in light of the described use for the composition Applicant maintains that it is unreasonable to conclude that the drug is being administered topically for local action rather than systemically thru the epithelial tissue that lines the vagina. It is very likely that the preferred mode of delivery is via aerosol (see e.g., claims 4, 5 and 7).

Zhou teaches a composition for inhibiting oral bacteria comprised of a polyphenol derivative, preferably a catechin derivative and at least one compound selected from the group consisting of a mogroside derivative composition, licorice extract and combinations thereof (col. 1, lines 40-48). Zhou does not teach or suggest a composition of matter comprised of a mixture of Free-B-Ring flavonoids and flavans. Zhou, like Xu also does not teach or suggest that any of the disclosed compositions and/or compounds would be useful in the treatment of inflammatory skin conditions. Rather, Zhou teaches that the disclosed compositions inhibit oral bacteria and are "effective in treating oral malodor and gum diseases, which helps prevent tooth decay and stomach acid reflux." (col. 1, line 64 - col. 2, line 1). Furthermore, as in the case of the Xu reference, there is no evidence to suggest that there would any overlap between indications requiring the use of the compositions taught by Zhou and those of the instantly claimed invention. Since Zhou teaches a composition for treatment of oral bacteria the suggested modes of administration include as a liquid solution such as tea or other beverage or oral rinse, as a drop

or gumdrops, chewing gum, breathe dots, toothpaste and the like (col 4, lines 31-36). Again there is no teaching or suggestion of a composition formulated for topical delivery to the skin.

As noted above, the claims of the instant invention are drawn to an anti-inflammatory composition comprising (1) an effective amount of an inflammation alleviating mixture of Free-B-Ring flavonoids and flavans; and (2) a pharmaceutically or cosmetically acceptable carrier suitable for administration to the skin selected from the group consisting of a lotion, a gel, an ointment, a cream, a soap and an emulsion, wherein the pharmaceutical or cosmetic composition alleviates inflammation when topically applied to the skin. There is no teaching or suggestion in either of the references cited by the Examiner, alone or in combination, of a composition comprised of a mixture of Free-B-Ring flavonoids and flavans. In fact, to date Applicant is unaware of any reports of a topical formulation combining exclusively Free-B-Ring flavonoids and flavans as the primary biologically active components for the treatment of any disease or condition, including those related to inflammatory conditions of the skin. There is also no evidence based on the cited art, and none has been provided by the Examiner, that one skilled in the art would combine the mixture as required in the present claims in an inflammation alleviating amount. The amount of compound needed for an antimicrobial would not necessarily be sufficient for the topical treatment of inflammation. Applicant maintains that it would not have been obvious to combine the antimicrobial composition taught by Xu with the antimicrobial composition taught by Zhou into a topical formulation for local delivery for use in the treatment of inflammatory skin conditions. As noted above, "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." In light of this, Applicant respectfully requests that the Examiner reconsider this rejection.

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: March 3, 2010

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Topical and Transdermal Drug Products

The Topical/Transdermal Ad Hoc Advisory Panel for the USP Performance Tests of Topical and Transdermal Dosage Forms: Clarence T. Ueda (Chair), Vinod P. Shah (USP Scientific Liaison), Kris Derdzinski, Gary Ewing, Gordon Flynn, Howard Maibach, Margareth Marques (USP Scientific Liaison),[a] Howard Rytting,[b] Steve Shaw, Kailas Thakker, and Avi Yacobi.

ABSTRACT This *Stimuli* article provides general information about the test methods that should be employed to ensure the quality and performance of topical and transdermal drug products. The term *topical drug products* refers to all formulations applied to the skin except transdermal delivery systems (TDS) or transdermal patches that will be addressed separately.

INTRODUCTION

Drug products topically administered via the skin fall into two general categories, those applied for local action and those for systemic effects. Local actions include those at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis. Common products in the former category include creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. Creams, ointments, and gels generally are referred to as semisolid dosage forms. The most common drug products applied to the skin for systemic effects are referred to as self-adhering transdermal drug delivery systems (TDS) or transdermal patches.

Two categories of tests, product quality tests and product performance tests, are performed with drug products to provide assurances of batch-to-batch quality, reproducibility, reliability, and performance. Product quality tests are performed to assess attributes such as assay, identification, content uniformity, pH, microbial limits, and minimum fill and are part of the compendial monograph. Product performance tests are conducted to assess drug release from the finished dosage form.

This *Stimuli* article provides general information about the test methods that should be employed to ensure the quality and performance of topical and transdermal drug products. The term *topical drug products* refers to all formulations applied to the skin except transdermal delivery systems (TDS) or transdermal patches that will be addressed separately.

Topical dosage forms include solutions (for which release testing is not indicated), collodion, suspensions, emulsions (e.g., lotions), semisolids (e.g., foams, ointments, pastes, creams, and gels), solids (e.g., powders and aerosols), and sprays. The physical characteristics of these dosage forms vary widely.

Therefore, the in vitro release test for those products also may differ significantly and may require different types of apparatus. At present, a product performance test exists only for semisolid formulations, specifically creams, ointments, and gels. That test employs the vertical diffusion cell (VDC) system. The VDC system is simple to operate and yields reliable and reproducible results when employed by properly trained laboratory personnel.

TDS or transdermal patches are physical devices applied to the skin and vary in their composition and method of fabrication. Therefore, they release their active ingredients by different mechanisms.

GLOSSARY OF TERMS

Definitions of topical drug products, some aspects related to the manufacture of these products, and a glossary of dosage form names commonly used can be found in General Information Chapter *Pharmaceutical Dosage Forms* ⟨1151⟩.

Collodion

Collodion (pyroxylin solution; see *USP* monograph), is a solution of nitrocellulose in ether and acetone, sometimes with the addition of alcohol. As the volatile solvents evaporate, a dry celluloid-like film is left on the skin. Because the medicinal use of a collodion depends on the formation of a protective film, the film should be durable, tenacious in adherence, flexible, and occlusive.

Creams

Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil-in-water emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.

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[b] Deceased.

Emulsions

Emulsions are viscid, multiphase systems in which one or more liquids are dispersed throughout another immiscible liquid in the form of small droplets. When oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, when water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets, and, ultimately, into a single separated phase. Emulsifying agents (surfactants) act by concentrating at the interface between the immiscible liquids, thereby providing a physical barrier that reduces the tendency for coalescence. Surfactants also reduce the interfacial tension between the phases, facilitating the formation of small droplets upon mixing. The term emulsion is not used if a more specific term is applicable, e.g., cream or ointment.

Foams

Foams are emulsified systems packaged in pressurized containers or special dispensing devices that contain dispersed gas bubbles, usually in a liquid continuous phase, that when dispensed has a fluffy, semisolid consistency.

Gels

Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid. When the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., Aluminum Hydroxide Gel, *USP*). In a two-phase system if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g., Bentonite Magma, *NF*). Both gels and magmas may be thixotropic, forming semisolids after standing and becoming liquid when agitated. They should be shaken before use to ensure homogeneity and should be labeled to that effect (see Topical Suspensions, below). Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid with no apparent boundary between the dispersed macromolecule and liquid.

Lotions

Although the term lotion may be applied to a solution, lotions usually are fluid, somewhat viscid emulsion dosage forms for external application to the skin. Lotions share many characteristics with creams. See Creams, Topical Solutions, and Topical Suspensions, herein.

Ointments

Ointments are semisolids intended for external application to the skin or mucous membranes. They usually contain less than 20% water and volatiles and more than 50% hydrocarbons, waxes, or polyols as the vehicle. Ointment bases recognized for use as vehicles fall into four general classes: hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases. Each therapeutic ointment possesses as its base one of these four general classes.

Hydrocarbon Bases—Hydrocarbon bases, known also as "oleaginous ointment bases," are represented by White Petrolatum and White Ointment (both *USP*). Only small amounts of an aqueous component can be incorporated into these bases. Hydrocarbon bases serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings. These bases are used chiefly for their emollient effects and are difficult to wash off. They do not "dry out" or change noticeably on aging.

Absorption Bases—This class of bases may be divided into two groups: the first consists of bases that permit the incorporation of aqueous solutions with the formation of a water-in-oil emulsion (e.g., Hydrophilic Petrolatum and Lanolin, both *USP*), and the second group consists of water-in-oil emulsions that permit the incorporation of additional quantities of aqueous solutions (Lanolin, *USP*). Absorption bases also are useful as emollients.

Water-removable Bases—Water-removable bases are oil-in-water emulsions (e.g., Hydrophilic Ointment, *USP*), and are more correctly called "creams" (see Creams, above). They also are described as "water-washable" because they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic purposes. Some medicaments may be more effective in these bases than in hydrocarbon bases. Other advantages of the water-removable bases are that they may be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

Water-soluble Bases—This group of so-called "greaseless ointment bases" comprises water-soluble constituents. Polyethylene Glycol Ointment, *NF* is the only pharmacopeial preparation in this group. Bases of this type offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as petrolatum, anhydrous lanolin, or waxes. They are more correctly called Gels (see Gels, above).

Choice of Base—The choice of an ointment base depends on many factors, such as the action desired, the nature of the medicament to be incorporated and its bioavailability and stability, and the requisite shelf life of the finished product. In some cases, it is necessary to use a base that is less than ideal in order to achieve the stability required. Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases that contain water, even though they may be more effective in the latter.

Ophthalmic Ointments

Ophthalmic ointments are semisolids for application to the eye. Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions, must meet the requirements under *Sterility Tests* ⟨71⟩, and must be free of large particles. The medicinal agent is added to the ointment base either as a solution or as a micronized powder.

Pastes

Pastes are semisolid dosage forms that contain a high percentage (often ≥ 50%) of finely dispersed solids with a stiff consistency intended for topical application. One class is made from a single-phase aqueous gel (e.g., Carboxymethylcellulose Sodium Paste, *USP*). The other class, the fatty pastes (e.g., Zinc Oxide Paste, *USP*), consists of thick, stiff ointments that do not ordinarily flow at body temperature and therefore serve as protective coatings over the areas to which they are applied.

Powders

Powders are solids or mixture of solids in a dry, finely divided state for external (or internal) use.

Sprays

Sprays are products formed by the generation of droplets of solution containing dissolved drug for application to the skin or mucous membranes. The droplets may be formed in a variety of ways but generally result from forcing the liquid through a specially designed nozzle assembly. One example of a spray dosage form is a metered-dose topical transdermal spray that delivers a precisely controlled quantity of solution or suspension on each activation.

Topical Aerosols

Topical aerosols are products that are packaged under pressure. The active ingredients are released in the form of fine liquid droplets or fine powder particles upon activation of an appropriate valve system. A special form is a metered-dose aerosol that delivers an exact volume (dose) per each actuation.

Topical Solutions

Topical solutions are liquid preparations, that usually are aqueous but often contain other solvents such as alcohol and polyols that contain one or more dissolved chemical substances intended for topical application to the skin, or, as in the case of Lidocaine Oral Topical Solution *USP*, to the oral mucosal surface.

Topical Suspensions

Topical suspensions are liquid preparations that contain solid particles dispersed in a liquid vehicle intended for application to the skin. Some suspensions labeled as "Lotions" fall into this category.

Transdermal Delivery Systems

Transdermal delivery systems (TDS) are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir that may have a drug release–controlling membrane, a contact adhesive applied to some or all parts of the system and the system/skin interface, and a protective liner that is removed before the patient applies the system. The dose of these systems is defined in terms of the release rate of the drug(s) from the system and surface area of the patch and is expressed as mass per unit time for a given surface area. With these drug products, the skin typically is the rate-controlling membrane for the drug input into the body. The total duration of drug release from the system and system surface area may also be stated.

TDS work by diffusion: The drug diffuses from the drug reservoir, directly or through the rate-controlling membrane and/or contact adhesive if present, and then through the skin into the general circulation. Typically, modified-release systems are designed to provide drug delivery at a constant rate so that a true steady-state blood concentration is achieved and maintained until the system is removed. Following removal of the system, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

PRODUCT QUALITY TESTS—GENERAL

The International Conference on Harmonization (ICH) Guidance Q6A (available at www.ich.org) recommends specifications (tests, procedures, and acceptance criteria) to ensure that commercialized drug products are safe and effective at release and during shelf life. Tests that are universally applied to ensure safety and efficacy include description, identification, assay, and impurities.

Description—A qualitative description of the dosage form should be provided. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate. It specifies the content or the label claim of the article.

Identification—Identification tests are discussed in *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. Identification tests should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structure that are likely to be present. Identity tests should be specific for the drug substances. The most conclusive test for identity is the infrared absorption spectrum (see *Spectrophotometry and Light-scattering* ⟨851⟩

and *Spectrophotometric Identification Tests* ⟨197⟩). If no suitable infrared spectrum can be obtained, other analytical techniques can be used. Near infrared (NIR) or Raman spectrophotometric methods also could be acceptable as the sole identification method of the drug product formulation (see *Near-infrared Spectrophotometry* ⟨1119⟩ and *Raman Spectroscopy* ⟨1120⟩). Identification solely by a single chromatographic retention time is not regarded as specific. However, the use of two chromatographic procedures for which the separation is based on different principles or a combination of tests in a single procedure can be acceptable. See *Chromatography* ⟨621⟩ and *Thin-layer Chromatographic Identification* ⟨201⟩.

Assay—A specific and stability-indicating test should be used to determine the strength (content) of the drug product. See *Antibiotics—Microbial Assays* ⟨81⟩, ⟨621⟩, or *Assay for Steroids* ⟨351⟩. In cases when the use of nonspecific assay is justified, e.g., *Titrimetry* ⟨541⟩, other supporting analytical procedures should be used to achieve overall specificity. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

Impurities—Process impurities, synthetic by-products, and other inorganic and organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product. These impurities are controlled by the drug substance and excipients monographs. Organic impurities arising from the degradation of the drug substance and those arising during the manufacturing process of the drug product should be monitored.

In addition to the universal tests listed above, the following tests may be considered on a case-by-case basis:

Physicochemical Properties—These are properties such as *pH* ⟨791⟩, *Viscosity* ⟨911⟩, and *Specific Gravity* ⟨841⟩.

Uniformity of Dosage Units—This test is applicable for TDS and for dosage forms packaged in single-unit containers. It includes both the mass of the dosage form and the content of the active substance in the dosage form. The test can be performed by either content uniformity or weight variation (see *Uniformity of Dosage Units* ⟨905⟩).

Water Content—A test for water content should be included when appropriate (see *Water Determination* ⟨921⟩).

Microbial Limits—The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. See *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩ and *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩.

Antimicrobial Preservative Content—Acceptance criteria for preservative content in multidose products should be established. They should be based on the levels of antimicrobial preservative necessary to maintain the product's microbiological quality at all stages throughout its proposed usage and shelf life (see *Antimicrobial Effectiveness Testing* ⟨51⟩).

Antioxidant Preservative Content—If antioxidant preservatives are present in the drug product, tests of their content normally should be determined.

Sterility—Depending on the use of the dosage form, e.g., ophthalmic preparations, sterility of the product should be demonstrated as appropriate (see *Sterility Tests* ⟨71⟩).

PRODUCT QUALITY TESTS FOR TOPICAL DRUG PRODUCTS

General product quality tests such as identification, assay, content uniformity (uniformity of dosage units), impurities, pH, water content, microbial limits, antimicrobial preservative content, antioxidant preservative content, and sterility should be performed for topical drug products as described above. In addition, specific tests for topical dosage forms, as described below, also should be conducted.

Viscosity—Rheological properties such as viscosity of semisolid dosage forms can influence their drug delivery. Viscosity may directly influence the diffusion rate of drug at the microstructural level. Yet semisolid drug products with relatively high viscosity still can exhibit high diffusion rates when compared to semisolid products of comparatively lower viscosity. These observations emphasize the importance of rheologic properties of semisolid dosage forms, specifically viscosity, on drug product performance.

Depending on its viscosity, the rheological behavior of a semisolid drug product may affect its application to treatment site(s) and consistency of treatment and thus the delivered dose. Therefore, maintaining reproducibility of a product's flow behavior at the time of release is an important product manufacturing control to maintain and demonstrate batch-to-batch consistency. Most semisolid dosage forms, when sheared, exhibit non-Newtonian behavior. Structures formed within semisolid drug products during manufacturing can show a wide range of behaviors, including shear thinning viscosity, thixotropy, and structural damage that may be irreversible or only partially reversible. In addition, the viscosity of a semisolid dosage form is highly influenced by such factors as the inherent physical structure of the product, product sampling technique, sample temperature for viscosity testing, container size and shape, and specific methodology employed in the measurement of viscosity.

A variety of methods can be used to characterize the consistency of semisolid dosage forms, such as penetrometry, viscometry, and rheometry. With all methods significant attention is warranted to the shear history of the sample. For semisolids, viscometer geometries typically fall into the following categories: concentric cylinders, cone-plates, and spindles. Concentric cylinders and spindles typically are used for more fluid, flowable semisolid

dosage forms. Cone-plate geometries are more typically used when the sample size is small or the test samples are more viscous and less flowable.

When contemplating what viscosity parameter(s) to test, one must consider the properties of the semisolid drug product both "at rest" (in its container) and as it is sheared during application. The rheological properties of the drug product at rest can influence the product's shelf life, and its properties under extensive shear can influence its spreadability and, therefore, its application rate that will affect the safety and efficacy of the drug product. Further, although it is necessary to precisely control the temperature of the test sample during the viscosity measurement, one should link the specific choice of the temperature to the intended use of the drug product (e.g., skin temperature for external application effects).

Because semisolid dosage forms frequently display non-Newtonian flow properties, formulators should give close attention to the shear history of the sample being tested, such as the shear applied during the filling operation, shear applied dispensing the product from its container, and shear introducing the sample into the viscometer. The point of reemphasizing this aspect is that considerable variability and many failures to meet specifications can be directly attributed to a lack of attention to this detail rather than a change of viscosity (or flow properties) of the drug product.

Tube (Content) Uniformity—Tube uniformity is the degree of uniformity of the amount of active drug substance among containers, i.e., tubes containing multiple doses of the semisolid topical product. The uniformity of dosage is demonstrated by assay of top, middle, and bottom samples (typically 0.25–1.0 g) obtained from a tube cut open to withdraw respective samples for drug assay.

Various topical semisolid products may show some physical separation at accelerated storage temperatures because emulsions, creams, and topical lotions are prone to mild separation due to the nature of the vehicle.

The following procedure should be followed for testing tube uniformity of semisolid topical dosage forms:

1. Carefully remove or cut off the bottom tube seal and make a vertical cut up the face of the tube. Then carefully cut the tube around the upper rim and pry open the two "flaps" to expose the semisolid.
2. At the batch release and/or designated stability time point remove and test 0.25- to 1.0-g samples from the top, middle, and bottom of a tube. If assay values for those tests are within 90.0% to 110.0% of the labeled amount of active drug, and the relative standard deviation (RSD) is not more than 6%, then the results are acceptable.
3. If at least 1 value of the testing described above is outside 90.0% to 110.0% of the labeled amount of drug and none is outside 85.0% to 115.0% and/or the RSD is more than 6%, then test an additional 3 randomly sampled tubes using top, middle, and bottom samples as described. Not more than 3 of the 12 determinations should be outside the range of 90% to 110.0% of the labeled amount of drug, none should be outside 85.0% to 115.0%, and the RSD should not be not more than 7%.
4. For very small tubes (e.g., 5 g or less), test only top and bottom samples, and all values should be within the range of 90.0% to 110.0% of the labeled amount of drug.

pH—When applicable, semisolid drug products should be tested for pH at the time of batch release and designated stability test time points for batch-to-batch monitoring. Because most semisolid dosage forms contain very limited quantities of water or aqueous phase, pH measurements may be warranted only as a quality control measure, as appropriate.

Particle Size—Particle size of the active drug substance in semisolid dosage forms is determined and controlled at the formulation development stage. When applicable, semisolid drug products should be tested for any change in the particle size or habit of the active drug substance at the time of batch release and designated stability test time points (for batch-to-batch monitoring) that could compromise the integrity and/or performance of the drug product, as appropriate.

Ophthalmic Dosage Forms—Ophthalmic dosage forms must meet the requirements of *Sterility* ⟨71⟩. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under *Sterility* ⟨71⟩, along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use, unless otherwise directed in the individual monograph or unless the formula itself is bacteriostatic (see *Added Substances* under *Ophthalmic Ointments* ⟨771⟩). The finished ointment must be free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* in ⟨771⟩. The immediate containers for ophthalmic ointments shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic ointments be sealed and tamper-proof so that sterility is assured at time of first use.

PRODUCT QUALITY TESTS FOR TOPICAL DRUG PRODUCTS

General product quality tests such as identification, assay, content uniformity (uniformity of dosage units), impurities, pH, water content, microbial limits, antimicrobial preservative content, antioxidant preservative content, and sterility should be performed for topical drug products. In addition, specific tests for topical dosage forms, such as viscosity, tube (content) uniformity, and particle size also should be conducted. For details, see General Chapter *Product Quality Tests: Topical and Transdermal Drug Products* ⟨3⟩.

PRODUCT PERFORMANCE TEST FOR TOPICAL DRUG PRODUCTS

A performance test for topical drug products must have the ability to measure drug release from the finished dosage form. It must be reproducible and reliable, and although it is not a measure of bioavailability, the performance test must be capable of detecting changes in drug release characteristics from the finished product. The latter have the potential to alter the biological performance of the drug in the dosage form. Those changes may be related to active or inactive/inert ingredients in the formulation, physical or chemical attributes of the finished formulation, manufacturing variables, shipping and storage effects, aging effects, and other formulation factors critical to the quality characteristics of the finished drug product.

Product performance tests can serve many useful purposes in product development and in postapproval drug product monitoring. They provide assurance of equivalent performance for products that have undergone postapproval raw material changes, relocation or change in manufacturing site, and other changes as detailed in the FDA *Guidance for Industry—SUPAC-SS: Nonsterile Semisolid Dosage Forms, Manufacturing Equipment Addendum,* Dec 1998, available at http://www.fda.gov/cder/guidance/1722dft.pdf.

Vertical Diffusion Cell Method

Theory—The vertical diffusion cell (VDC) system is a simple, reliable, and reproducible means of measuring drug release from semisolid dosage forms. A thick layer of the test semisolid is placed in contact with a reservoir. Diffusive communication between the delivery system and the reservoir takes place through an inert, highly permeable support membrane. The membrane keeps the product and the receptor medium separate and distinct. Membranes are chosen to offer the least possible diffusional resistance and not to be rate controlling. Samples are withdrawn from the reservoir at various times. In most cases, a five- to six-hour time period is all that is needed to characterize drug release from a semisolid, and when this is the case samples usually are withdrawn hourly.

After a short lag period, release of drug from the semisolid dosage form in the VDC system is kinetically describable by diffusion of a chemical out of a semi-infinite medium into a sink. The momentary release rate tracks the depth of penetration of the forming gradient within the semisolid. Beginning at the moment when the receding boundary layer's diffusional resistance assumes dominance of the kinetics of release, the amount of the drug released, M, becomes proportional to $\sqrt{t}$ (where t = time) for solution, suspension, or emulsion semisolid systems alike. The momentary rate of release, dM/dt, becomes proportional to $1/\sqrt{t}$, which reflects the slowing of drug release with the passage of time. The reservoir is kept large so that drug release is into a medium that remains highly dilute over the entire course of the experiment relative to the concentration of drug dissolved in the semisolid. In this circumstance, drug release is said to take place into a diffusional sink.

When a drug is totally in solution within the dosage form, the amount of drug released as a function of time can be described by:

$$M = 2 \cdot Co \sqrt{\frac{D \cdot t}{\pi}}$$

where:

M = amount of drug released into the sink per cm²
Co = drug concentration in releasing matrix
D = drug diffusion coefficient through the matrix.

A plot of M vs $\sqrt{t}$ will be linear with a slope of

$$2 \cdot Co \sqrt{\frac{D}{\pi}}$$

The following equation describes drug release when the drug is in the form of a suspension within the dosage form:

$$M = \sqrt{2 \cdot Dm \cdot Cs \left(Q - \frac{Cs}{2} \right) t}$$

where

Cs = drug solubility in the releasing matrix
Dm = drug diffusion coefficient in the semisolid matrix
Q = total amount of the drug in solution and suspended in the matrix.

When $Q >> Cs$, the previous equation simplifies to:

$$M = \sqrt{2 \cdot Q \cdot Dm \cdot Cs \cdot t}$$

A plot of M vs $\sqrt{t}$ will be linear with a slope of $\sqrt{2QDmCs}$.

Coarse particles may dissolve so slowly that the moving boundary layer recedes to some extent behind the particles. That situation introduces noticeable curvature in the $\sqrt{t}$ plot because of a particle size effect. During release rate experiments, every attempt should be made to keep the composition of the formulation intact over the releasing period.

In Vitro Drug Release Using the VDC—A VDC system is used to determine in vitro release of semisolid (cream, ointment, and gel) preparations. Typically, 200–400 mg of a cream, ointment, or gel is spread evenly over a suitable synthetic inert support membrane. The membrane, with its application side up, is placed in a vertical diffusion cell (typically of 15-mm diameter orifice), e.g., a Franz cell. The release rate experiment is carried out at 32 ± 1 °C, except in the case of vaginal creams for which the temperature should be 37 ± 1 °C. Sampling generally is performed over 4–5 hours, and the volume sampled is replaced with fresh receptor medium. To achieve sink conditions, the receptor medium must have a high capacity to dissolve or carry away the drug, and the receptor media should not exceed 10% of Cs (drug solubility in

the releasing matrix) at the end of the test. The test is done with groups of 6 cells. Results from 12 cells, 2 runs of 6 cells, are used to document the release rate.

Application of Drug Release—The drug release results can be utilized for purposes such as ensuring product sameness after scale-up and post-approval related changes or successive batch release comparison.

The VDC assembly consists of two chambers, a donor chamber and a receptor chamber, separated by a donor compartment and held together by a clamp (see *Figure 1*). This type of cell is commonly used for testing the in vitro release rate of topical drug products such as creams, gels, and ointments. Alternative diffusion cells that conform to the same general design and size can be used.

The VDC body normally is made from borosilicate glass, although different materials may be used to manufacture the body and other parts of the VDC assembly. None of the materials should react with or absorb the test product or samples.

In the donor compartment, the semisolid dosage form sample sits on a synthetic membrane within the cavity of the dosage compartment that is covered with a glass disk.

The diameters of the orifices of the donor chamber and the dosage compartment, which defines the dosage delivery area for the test, should be sized within ± 5% of the specified diameter. The receptor chamber orifice should never be smaller than the orifice of the donor chamber and should be fabricated to the same size as the donor chamber orifice. The design of the VDC should facilitate proper alignment of the dosage compartment and receptor orifices.

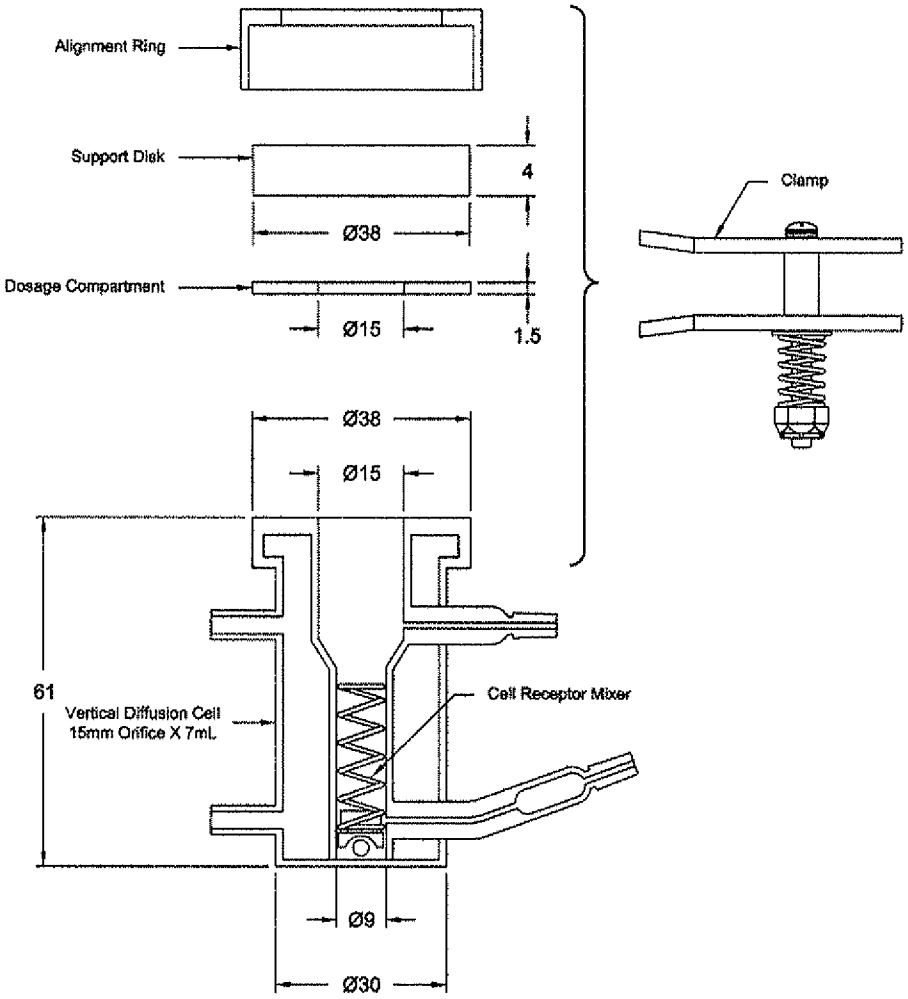


Figure 1. Vertical diffusion cell. (All measurements are expressed in mm unless noted otherwise).

The thickness of the dosage compartment normally is 1.5 mm. This thickness should be sized within ± 10% of the specified thickness.

The cell body should be manufactured consistently, with uniform height and geometry. Cells should appear the same, and their internal receptor volumes should fall within ± 20% of their specified volume.

Volume—Before conducting testing, determine the true volume of each receptor chamber in the VDC. The volume of each VDC should be determined with the internal stirring device in place.

Temperature—The temperature of the receptor media during the test should remain within ± 1.0 °C of the target temperature (typically 32 °C).

Speed—The rotational speed tolerance is ± 10% from the target speed (normally 600–800 rpm). The speed selected should ensure adequate mixing of the receptor media during the test.

Sampling Time—Samples should be taken at the specified times within a tolerance of ± 2% or ± 2 min, whichever is greatest.

Qualification—Unless otherwise specified in the individual monograph, the qualification of the apparatus is demonstrated by verifying the test temperature and speed requirements are met, along with a performance verification test (PVT). The PVT is passed if two tests of 6 cells comply with FDA's *SUPAC-SS* requirements of a 90% confidence interval. The PVT is performed by one analyst testing the specified reference standard in duplicate. The first test with 6 cells is performed and is defined as the reference. The second test of 6 cells is defined as the test. The PVT is passed if the second test passes the 90% confidence interval with reference to the first reference test.

Procedure—Unless otherwise specified in the individual monograph, degas the medium using an appropriate technique. With the stirring device in place, fill the VDC with the specified media and allow time for it to come to a temperature of 32 °C. If necessary, saturate the membrane in the specified media (generally receptor media) for 30 min. Place the membrane on the dosage compartment and invert. Apply the material that will be tested into the cavity of the dosage compartment, and spread the material out to fill the entire cavity of the dosage compartment.

Assemble each of the prepared dosage compartments to each VDC with the membrane down and in contact with the receptor media. During this application it is important to ensure that there are no bubbles under the membrane. When all dosage compartments and the remaining components are in place, turn on the stirring device, which constitutes time zero.

Follow the specified sampling procedure and collect an aliquot from each VDC for analysis. Ensure that during the sampling process bubbles are not introduced into the cell. Exercise care during sampling and replenishment of the medium in order not to introduce bubbles.

With some cells it is acceptable to have up to three bubbles under the membrane if the bubbles are less than 1 mm in diameter. With some cells, bubbles may be removed from the receptor chamber during the test by tipping the cell as long as this process is required only one time per position.

Calculation of Rate (Flux) and Amount of Drug Released

Creams and ointments are considered extended-release preparations. Their drug release largely depends on the formulation and method of preparation. The release rate of a given drug product from different manufacturers is likely to be different. It is assumed that the drug release of the product is linked to the clinical batch.

Unless otherwise specified in the individual monograph, the release requirements are met if the following have been achieved:

The *Amount Released* (µg/cm²) at a given time (t_1, t_2, etc.) is calculated for each sample as follows:

$$\text{Amount Released}_{t_1} = \frac{A_u}{A_s} \cdot C_s \cdot 1{,}000 \cdot \frac{V_c}{A_o}$$

$$\text{Amount Released}_{t_2} = \frac{A_u}{A_s} \cdot C_s \cdot 1{,}000 \cdot \frac{V_c}{A_o} + \left(AR_{t_1} \cdot \frac{V_s}{V_c} \right)$$

$$\text{Amount Released}_{t_n} = \frac{A_u}{A_s} \cdot C_s \cdot 1{,}000 \cdot \frac{V_c}{A_o} + \sum_{i=1}^{n-1} \left(AR_{t_{n-1}} \cdot \frac{V_s}{V_c} \right)$$

where

A_u = Area of the current sample
A_s = Average area of the standard
C_s = Concentration of the standard, mg/mL
V_c = Volume of the diffusion cell, mL
AR = Amount released, µg/cm²
A_o = Area of the orifice, cm²
V_s = Volume of the sample aliquot, mL.

For each cell the individual amount released is plotted vs time, and the slope of the resulting line (rate of drug release, flux) is determined. The average of 6 + 6 slopes represents the drug release of the dosage form and serves as the standard for the drug product.

Application of Drug Release

The drug release results can be utilized for purposes such as ensuring product sameness after *SUPAC-SS*–related changes or successive batch release comparison. This is illustrated by the following example where the initial drug batch is referred to as *Reference Batch* (R) and the changed or subsequent batch is referred to as *Test Batch* (T). The individual amount released from R is plotted vs time, and the resulting slope is determined. These are the reference slopes. The process is repeated to determine the test slopes.

The T/R Ratios are calculated for each Test-to-Reference Slope. This is most easily done by creating a table in which the Test Slopes are listed down the left side of the table and the Reference Slopes are listed across the

top of the table. The T/R ratios are then calculated and entered in the body of the table where the rows and columns intersect (*Table 1*).

After the T/R Ratios have been calculated they are ordered from lowest to highest. The 8th and 29th T/R Ratios are extracted and converted to percent (multiply by 100). To pass the first stage these ratios must fall within the range of 75% to 133.33%.

If the results do not meet this criterion, the FDA *SUPAC-SS* guidance requires that 4 more tests of 6 cells each must be run, resulting in 12 additional slopes per product tested. The T/R ratios are calculated for all 18 slopes per product tested. All 324 individual T/R Ratios are calculated and ordered lowest to highest. The 110th and the 215th ratios are evaluated against the specification of 75% to 133.33%.

No third stage is suggested.

PVT Method for USP Hydrocortisone Cream Reference Standard

Materials and Equipment

USP Hydrocortisone Cream Reference Standard; 25-mm, 0.45-µm hydrophilic polysulfone [NOTE—a suitable filter is Tuffryn available from www.pall.com] membrane filters; vacuum filtration apparatus consisting of a filter holder with a medium or fine-porosity sintered glass holder base, funnel with a 250-mL capacity, and magnetic stirrer; small and smooth jeweler's forceps; depression porcelain color plate; Diffusion Cell System with 6 diffusion cells and temperature control circulator; and sampling syringe or device and collection vials.

Procedure

Receptor Medium Preparation

Mix 60 mL of USP Alcohol with 140 mL of water to prepare a 30% alcoholic media. Degas the media by filtering through a 47-mm, 0.45-µm membrane by vacuum filtration. Assemble the filtration apparatus placing a magnetic stir bar (approximately 1in × 0.25 in) in the receiving flask. Place the apparatus on a magnetic stirring plate, and spin the bar at a moderate rate. Apply vacuum and pass the media through the filter while stirring. After all media have passed through the filter, continue stirring while maintaining a vacuum for 2 min. Applying vacuum and stirring beyond 2 min may change the composition of the water–alcohol media. Care should be taken to ensure that the period of time that the media is under vacuum after the filtration is complete is limited to 2 min.

Immediately transfer the degassed receptor medium to a suitable receptor medium bottle and stopper. Place the receptor medium bottle in the jacketed beaker and allow the media to equilibrate for 30 min before use.

Preparation of Apparatus

Set the circulating bath to a temperature (typically 32.5 °C) that will maintain the temperature in the diffusion cells at 32 °C during the test. Place the appropriate magnetic stirrer in each diffusion cell. Allow the system to equilibrate for at least 30 min before beginning the test.

Sample Preparation

Carefully lift one membrane at its very edge with jeweler's forceps. Place the membrane on a paper tissue, and blot any extreme excess solution (a slight excess solution is desired). Carefully place the membrane in the center of the dosage compartment. Place the dosage compartment, with the membrane centered on the underside, onto a tissue and press down on the compartment. Apply an appropriate amount of Hydrocortisone Cream Reference Standard (between 200 mg and 400 mg) on top of the membrane and inside of the dosage compartment cavity. Use a spatula to carefully smooth the material over the membrane, filling the entire cavity of the dosage compartment. Wipe any excess material from the surface of the dosage compartment. Repeat for a total of 6 sample preparations.

Performing the Test

Fill the diffusion cells with receptor media, and allow time to equilibrate to 32 °C. Ensure that the stirrers are not rotating and that there is a positive meniscus covering the complete top of each diffusion cell. Place the glass disk on top of the dosage compartment against the sample. Place the dosage compartment/glass disk assembly on the top of the diffusion cell, avoiding bubbles. Inspect under the membrane for bubbles. Assemble the cell. Repeat for each cell.

Begin the test according to the following test parameters: temperature: 32 °C; stir speed: 600–800 rpm; total test time: 6 h; sampling times: 1, 2, 3, 4, and 6 h.

Table 1. Calculation of T/R Ratios

	RS1	RS2	RS3	RS4	RS5	RS6
TS1	TS1/RS1	TS1/RS2	TS1/RS3	TS1/RS4	TS1/RS5	TS1/RS6
TS2	TS2/RS1	TS2/RS2	TS2/RS3	TS2/RS4	TS2/RS5	TS2/RS6
TS3	TS3/RS1	TS3/RS2	TS3/RS3	TS3/RS4	TS3/RS5	TS3/RS6
TS4	TS4/RS1	TS4/RS2	TS4/RS3	TS4/RS4	TS4/RS5	TS4/RS6
TS5	TS5/RS1	TS5/RS2	TS5/RS3	TS5/RS4	TS5/RS5	TS5/RS6
TS6	TS6/RS1	TS6/RS2	TS6/RS3	TS6/RS4	TS6/RS5	TS6/RS6

Sampling Procedure

At each of the stated sampling times, collect a sample from each cell as follows:

Stop the stirrer 30 sec before sampling. Repeat sampling procedure for each cell in order from 1 to 6. After the sixth cell has been sampled, resume the stirrer rotation.

High-performance Liquid Chromatography (HPLC) Hydrocortisone Analysis

USP Hydrocortisone Cream Reference Standard; acetonitrile, HPLC grade; water, HPLC grade; USP alcohol, 95%; 47-mm, 0.45-µm hydrophilic polysulfone membrane filters [NOTE—a suitable filter is Tuffryn available from www.pall.com]; HPLC System with UV detector capable of 10-µL injections; 50 mm × 3.9 mm column that contains 5 µm packing L1.

Procedure

Mobile Phase Preparation

Prepare and degas a sufficient volume of mobile phase to complete the analysis of the samples collected. For each 1 L of mobile phase mix 200 mL of acetonitrile with 800 mL of water. If necessary, adjust the mobile phase composition to achieve an approximate retention time of 7 min for the hydrocortisone peak.

Standard Preparation

Obtain a portion of appropriately dried Hydrocortisone Cream Reference Standard. Prepare a stock hydrocortisone standard solution at a concentration of approximately 0.20 mg/mL in USP alcohol. A solution of 20 mg hydrocortisone in 100 mL of USP alcohol is suggested for the stock standard preparation. Prepare a working standard solution by making a 5-fold dilution of the stock standard in a solution of 30:70 USP alcohol/water mixture. For example, dilute 2 mL to 10 mL.

Chromatographic Conditions

Wavelength—242 nm; flow rate: 1 mL/min; injection volume: 10 µL; run time: 10 min; column: 50 mm × 3.9 mm C-18, 5-µm (Symmetry); mobile phase: 20/80 acetonitrile/water. Begin the analysis by making 5 replicate injections of the working hydrocortisone standard solution for system suitability.

System Suitability Requirements—Relative standard deviation: < 2%; tailing factor: NMT 1.5. Make single injections of each of the samples obtained during the in vitro release testing. Bracket injections of samples with single standard injections after the analysis of the 2-h samples, 4-h samples, and 6-h samples. Calculate the results as specified.

Other Test Systems

Other diffusion-type cell devices are available as potential apparatus for drug release testing from topical/dermal drug products. However, only limited data are available for these devices. USP will consider these devices for inclusion in this General Chapter after they are validated and collaborative study data have been evaluated. The devices currently include:

Modified Holding Cell—A sample of semisolid dosage form is placed in an inert holding cell with a suitable membrane separating the dosage form from the receptor medium. The holding cell is positioned at the bottom of a modified, reduced-volume dissolution vessel of the USP Apparatus 2 type and is stirred with a mini paddle.

USP Apparatus 4 (Flow-through Cell) with a Trans-cap Semisolid Cell—A sample of the semisolid dosage form is placed in the trans-cap cell with a suitable membrane separating the dosage form from the receptor medium. The trans-cap cell with membrane facing upward is inserted into the 22.6-mm flow cell of USP Apparatus 4 (Flow-through Cell).

Extraction Cell—A sample of the semisolid dosage form is placed in an inert extraction cell with a suitable membrane separating the dosage form from the receptor medium. The test is performed using the USP Apparatus 2 assembly with the extraction cell positioned at the bottom of the dissolution vessel.

Product Quality Tests for Transdermal Delivery Systems

TDS are physical devices that deliver their active ingredient at a fixed rate over a prolonged period of time, e.g., from days to as long as one month. Their methods of delivery or release mechanisms vary significantly because of differences in their composition and fabrication. TDS systems can be categorized as (1) liquid form, fill, and seal systems, (2) peripheral adhesive systems, or (3) matrix systems. The latter two categories include the subcategories of monolithic, matrix, multi-laminate, and drug-in-adhesive systems. Moreover, recent advances in the design of novel transdermal drug delivery systems has expanded the list of basic TDS categories further, including, systems that employ iontophoresis, heat-assisted drug delivery, or micro-needles.

In all three principal TDS categories, the drug is in solution or suspension. Factors that can influence drug release and, therefore, the performance of TDS dosage forms include changes in formulation composition involving the adhesive, solvents, viscosity-modifying agents, permeation enhancers, and changes in the dosage form's semipermeable film or laminate.

The product quality tests for transdermal drug delivery system include assay, content uniformity, homogeneity, and adhesive test.

Uniformity of dosage units—This test is applicable for transdermal systems and for dosage forms that are packaged in single-unit containers. It includes both the mass of the dosage form and the content of the active substance in the dosage form. It can be done by either content uniformity or weight variation (see ⟨905⟩).

Assay of excipient(s) critical to the performance of the product should be considered; e.g., residual solvent content can affect certain patches.

Adhesive Test—Three types of adhesive tests generally are performed to ensure the performance of the TDS dosage forms. These are the peel adhesion test, tack test, and shear strength test. The peel adhesion test measures the force required to peel away a transdermal patch attached to a stainless steel test panel substrate at panel angles of 90° or 180° following a dwell time of 1 min and peel rate of 300 mm/min.

The tack test is used to measure the tack adhesive properties of TDS dosage forms. With this test a probe touches the adhesive surface with light pressure, and the force required to break the adhesion after a brief period of contact is measured.

The shear strength or creep compliance test is a measure of the cohesive strength of TDS dosage forms. Two types of shear testing are performed: dynamic and static. During dynamic testing the TDS is pulled from the test panel at a constant rate. With the static test the TDS is subjected to a shearing force by means of a suspended weight.

Leak Test—A test that is discriminating and capable of detecting sudden drug release, such as leakage, from the TDS should be performed. Although form, fill, and seal TDS are more likely to display leak problems, all TDS should be checked for sudden drug release (dose dumping) during release testing of the dosage form.

Product Performance Tests for TDS

As with topical drug products, a performance test for transdermal drug products also must have the ability to measure drug release from the finished dosage form, must be reproducible and reliable, and must be capable of detecting changes in drug release characteristics from the finished product. Again, the latter have the potential to alter the desired pharmacologic effect(s) of the active ingredient. Such changes could be related to active or inactive/inert ingredients in the formulation or physical dosage form, physical or chemical attributes of the finished preparation, manufacturing variables, shipping and storage, age, and other critical-to-quality characteristics of the finished dosage form.

When based on sound scientific principles, product performance tests can be used for pre- and postmanufacturing purposes such as during the product research and development phase, as a basic quality control tool, for demonstrating product similarity, or for demonstrating compliance with FDA guidelines (e.g., approval and postapproval changes in the dosage form).

In vitro drug release methods for transdermal patches include USP Apparatus 5 (Paddle over Disk Method), Apparatus 6 (Rotating Cylinder Method), or Apparatus 7 (Reciprocating Holder Method). In general, it has been found that Apparatus 5, a modified paddle method, is simpler and is applicable for most types, sizes, and shapes of TDS.

Apparatus 5 (Paddle over Disk Method)

Apparatus—Use the paddle and vessel assembly from *Apparatus 2* as described in *Dissolution* ⟨711⟩, with the addition of a stainless steel disk assembly (*1*) designed for holding the transdermal system at the bottom of the vessel. Other appropriate devices may be used, provided they do not absorb, react with, or interfere with the specimen being tested (*2*). The temperature should be maintained at 32 ± 0.5 °C. During the test maintain a distance of 25 ± 2 mm between the paddle blade and the surface of the disk assembly. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any dead volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned so that the release surface is parallel with the bottom of the paddle blade (see *Figure 2*).

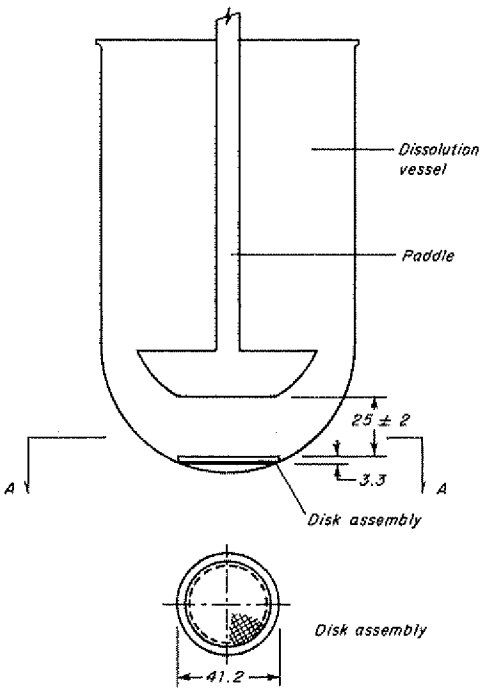


Fig. 2. Paddle over Disk. (All measurements are expressed in mm unless noted otherwise.)

Apparatus Suitability Test and Dissolution Medium—Proceed as directed for *Apparatus 2* in ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel, assemble the apparatus without the disk assembly, and equilibrate the medium to 32 ± 0.5 °C. Apply the transdermal system to the disk assembly, ensuring that the release surface of the system is as flat as possible. The system may be attached to the disk

by applying a suitable adhesive (*3*) to the disk assembly. Dry for 1 min. Press the system, release surface side up, onto the adhesive-coated side of the disk assembly. If a membrane (*4*) is used to support the system, it should be applied in such a way that no air bubbles occur between the membrane and the release surface. Place the disk assembly flat at the bottom of the vessel with the release surface facing up and parallel to the edge of the paddle blade and surface of the *Dissolution Medium*. The bottom edge of the paddle should be 25 ± 2 mm from the surface of the disk assembly. Immediately start operation of the apparatus at the rate specified in the monograph. At each sampling time interval, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the blade, not less than 1 cm from the vessel wall. Perform the analysis on each sampled aliquot as directed in the individual monograph, correcting for any volume losses, as necessary. Repeat the test with additional transdermal systems.

Sampling Time—The test time points, generally three, are expressed in hours. Specimens should be withdrawn within a tolerance of ± 15 min or ± 2% of the stated time; select the tolerance that results in the narrowest time interval.

In Vitro Release Criteria—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range, and none of the units is outside the stated range by more than 20% of the average of the stated range.

Apparatus 6 (Rotating Cylinder Method)

Apparatus—Use the vessel assembly from *Apparatus 1* as described in ⟨711⟩, but replace the basket and shaft with a stainless steel cylinder stirring element and maintain the temperature at 32 ± 0.5 °C during the test. The shaft and cylinder components of the stirring element are fabricated from stainless steel to the specifications shown in *Figure 3*. The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

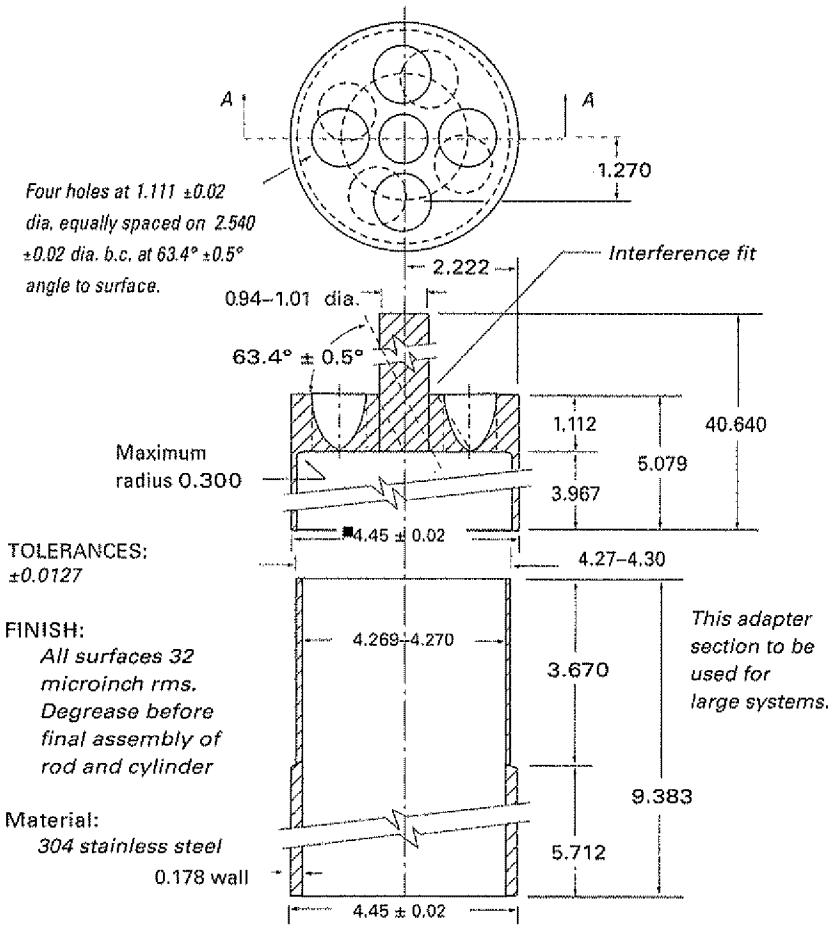


Fig. 3. Cylinder Stirring Element (*5*). (All measurements are expressed in cm unless noted otherwise.)

Dissolution Medium—Use the medium specified in the individual monograph (see ⟨711⟩).

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, and equilibrate the *Dissolution Medium* to 32 ± 0.5 °C. Unless otherwise directed in the individual monograph, prepare the test system before the test as follows:

Remove the protective liner from the system, and place the adhesive side on a piece of Cuprophan (*4*) that is not less than 1 cm larger on all sides than the system. Place the system, Cuprophan-covered side down, on a clean surface, and apply a suitable adhesive (*3*) to the exposed Cuprophan borders. If necessary, apply additional adhesive to the back of the system. Dry for 1 min. Carefully apply the adhesive-coated side of the system to the exterior of the cylinder so that the long axis of the system fits around the circumference of the cylinder. Press the Cuprophan covering to remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a quantity of *Dissolution Medium* for analysis from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating cylinder, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug delivery systems.

Sampling Time—Proceed as directed for Apparatus 5.

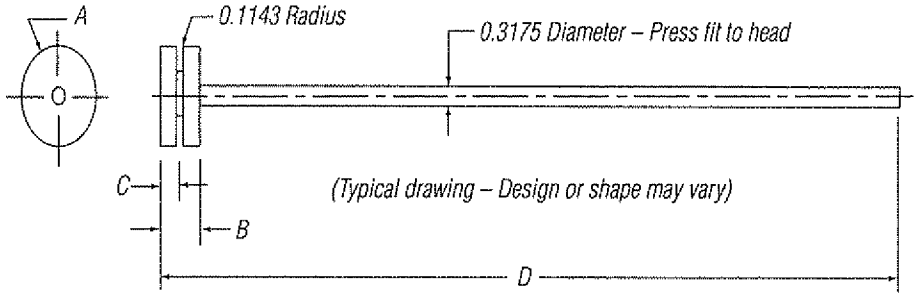
In Vitro Release Criteria—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Apparatus 7 (Reciprocating Holder Method)

Apparatus—The assembly consists of a set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material (*6*), a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels auto-

matically if desired, and a set of suitable sample holders [see *Figure 4* (*2*) and *Figures 5a* and *5b*). The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature, *T*, inside the containers at 32 ± 0.5 °C or within the allowable range, as specified in the individual monograph, during the test. No part of the assembly, including the environment in which the assembly is placed, should contribute motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating sample holder.

An apparatus that permits observation of the system and holder during the test is preferable. Use the size container and sample holder specified in the individual monograph.



Dimensions are in centimeters

	HEAD				ROD		O-RING
System[a]	*A (Diameter)*	*B*	*C*	Material[b]	*D*	Material[c]	*(not shown)*
1.6cm^2	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5cm^2	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5cm^2	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7cm^2	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10cm^2	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[a] Typical system sizes.
[b] SS/VT=Either stainless steel or virgin Teflon.
[c] SS/P=Either stainless steel or Plexiglas.

Fig. 4. Reciprocating Disk Sample Holder (*7*).

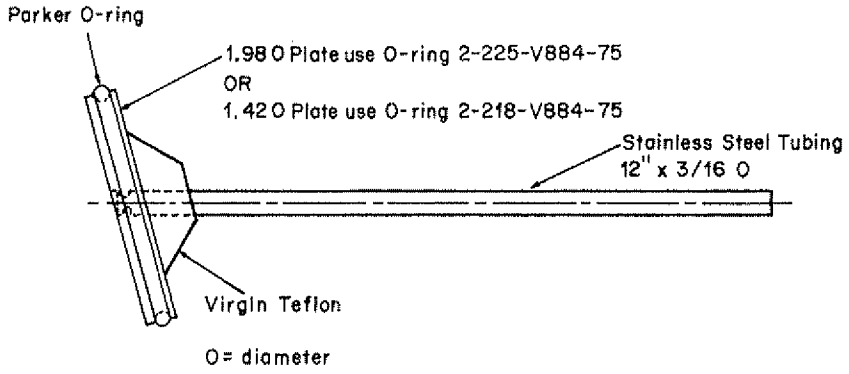


Fig. 5a. Transdermal System Holder—Angled Disk.

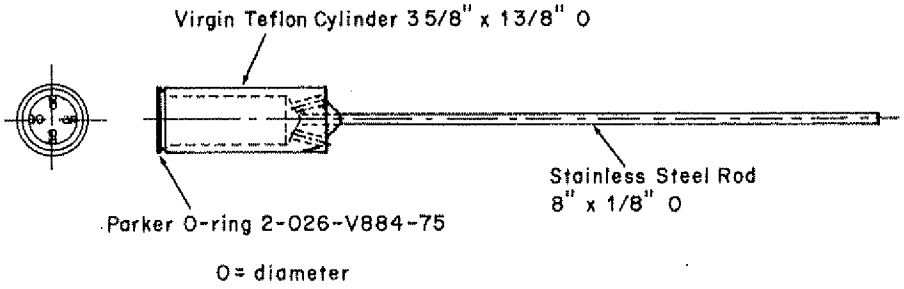


Fig. 5b. Transdermal System Holder—Cylinder.

Sample Preparation A—Attach the system to be tested to a suitable sample holder with 2-cyano acrylate glue.

Sample Preparation B—Press the system onto a dry, unused piece of Cuprophan (*4*), nylon netting, or equivalent with the adhesive side against the selected substrate, taking care to eliminate air bubbles between the substrate and the release surface. Attach the system to a suitably sized sample holder with a suitable O-ring so that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade.

Sample Preparation C—Attach the system to a suitable holder as described in the individual monograph.

Dissolution Medium—Use the *Dissolution Medium* specified in the individual monograph (see ⟨711⟩).

Procedure—Suspend each sample holder from a vertically reciprocating shaker so that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container preequilibrated to temperature, *T*. Reciprocate at a frequency of about 30 cycles/min with an amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution containers from the bath, cool to room temperature, and add sufficient solution (water in most cases) to correct for evaporative losses. Perform the analysis as directed in the individual monograph. Repeat the test with additional drug delivery systems as required in the individual monograph.

Sampling Time—Proceed as directed for Apparatus 5.

In Vitro Release Criteria—Drug release should be measured at least at 3 time points, first time point around 1 hour, second around 50% of total drug release, and third around 85% drug release. Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the active ingredients released from the system conform to *Acceptance Table 1* under *Dissolution* ⟨711⟩ for transdermal drug delivery systems, or as specified in the individual monograph. Continue testing through the three levels unless the results conform at either L_1 or L_2.

NOTE

This *Stimuli* article is subdivided into 2 chapters: *Product Quality Tests: Topical and Transdermal Drug Products* ⟨3⟩ and *Product Performance Tests: Topical and Transdermal Drug Products* ⟨725⟩. Both of these appear elsewhere in this issue of *Pharmacopeial Forum*.

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REFERENCES

1. Disk assembly (stainless support disk) is available from www.millipore.com.
2. A suitable device is the watchglass-patch-polytef mesh sandwich assembly available as the Transdermal Sandwich from www.hansonresearch.com.
3. Use Dow Corning, MD7-4502 Silicone Adhesive 65% in ethyl acetate, or the equivalent.
4. Use Cuprophan, Type 150 pm, 11 ± 0.5-µm thick, an inert, porous cellulosic material, which is available from www.medicell.co.uk or www.varianinc.com.
5. The cylinder stirring element is available from www.varianinc.com.
6. The materials should not sorb, react with, or interfere with the specimen being tested.
7. The reciprocating disk sample holder is available at www.varianinc.com.